

Tables and figures

Table 1 Baseline characteristics of patients before and after propensity score matching

	Before propensity score matching			After propensity score matching		
	Untreated	Treated	Standardized difference	Untreated	Treated	Standardized difference
N	31846	3900		7800	3900	
Age, mean±sd	81.1±9.4	79.4±8.5	0.186	79.4 ±10.0	79.4±8.5	0.004
Female, n (%)	22043 (69.2)	3087 (79.2)	0.229	6150 (78.8)	3087 (79.2)	0.008
Medical history, n (%)						
Cogestive heart failure	3191 (10.0)	288 ( 7.4)	0.094	610 ( 7.8)	288 ( 7.4)	0.016
Stroke	4380 (13.8)	422 (10.8)	0.089	839 (10.8)	422 (10.8)	0.002
Ischaemic heart disease	3748 (11.8)	373 ( 9.6)	0.071	786 (10.1)	373 ( 9.6)	0.017
Atrial fibrillation	2631 ( 8.3)	263 ( 6.7)	0.058	541 ( 6.9)	263 ( 6.7)	0.008
Embolism	47 ( 0.1)	3 ( 0.1)	0.021	7 ( 0.1)	3 ( 0.1)	0.004
Chronic Obstructive Pulmonary Disease	2969 ( 9.3)	341 ( 8.7)	0.02	699 ( 9.0)	341 ( 8.7)	0.008
Diabetes mellitus	6542 (20.5)	872 (22.4)	0.044	1710 (21.9)	872 (22.4)	0.01
Liver disease	235 ( 0.7)	20 ( 0.5)	0.029	39 ( 0.5)	20 ( 0.5)	0.002
Chronic kidney disases	1555 ( 4.9)	101 ( 2.6)	0.121	180 ( 2.3)	101 ( 2.6)	0.018
Rheumatic/collagen disorders	183 ( 0.6)	67 ( 1.7)	0.108	115 ( 1.5)	67 ( 1.7)	0.019
Dementia	2688 ( 8.4)	133 ( 3.4)	0.214	230 ( 2.9)	133 ( 3.4)	0.026
Osteoporosis	1393 ( 4.4)	413 (10.6)	0.238	786 (10.1)	413 (10.6)	0.017
Other fractures	3145 ( 9.9)	458 (11.7)	0.06	954 (12.2)	458 (11.7)	0.015
Paget's disease of bone	9 ( 0.0)	0 ( 0.0)	0.024	0 ( 0.0)	0 ( 0.0)	-
Fall	30997 (97.3)	3823 (98.0)	0.046	7627 (97.8)	3823 (98.0)	0.017

Table 2 Crude risk estimate of mortality in patients treated with anti-osteoporosis medications before propensity score matching

## A) All-cause mortality

Group	N	Short-term				Long-term			
		No. of death/py	Mortality rate, per 100 py	Relative risk (95% CI)	P	No. of death/py	Mortality rate, per 100 py	Relative risk (95% CI)	P
Untreated	31846	4036/29596	13.6	-	-	17977/135043	13.3	-	-
Treated	3900	217/3788	5.7	0.42 (0.37-0.48)	<0.001	1478/18599	7.9	0.6 (0.56-0.63)	<0.001
Stratified by individual drug									
Alendronate	2739	126/2608	4.8	0.35 (0.3-0.42)	<0.001	901/11852	7.6	0.57 (0.53-0.61)	<0.001
Ibandronate	541	26/479	5.4	0.4 (0.27-0.58)	<0.001	203/2532	8	0.6 (0.52-0.68)	<0.001
Risedronate	108	5/95	5.3	0.38 (0.16-0.92)	0.032	34/518	6.6	0.49 (0.35-0.68)	<0.001
Zoledronate	141	9/130	6.9	0.51 (0.26-0.97)	0.042	29/447	6.5	0.5 (0.34-0.71)	<0.001
Denosumab	30	1/28	3.6	0.26 (0.04-1.86)	0.18	6/79	7.6	0.59 (0.26-1.31)	0.193
Raloxifene	7	2/6	33.3	2.31 (0.58-9.23)	0.237	3/28	10.7	0.8 (0.26-2.47)	0.692
HRT	1	0/1	0	-	-	0/10	0	-	-
Salcatonin	166	27/124	21.8	1.58 (1.08-2.31)	0.018	84/513	16.4	1.23 (0.99-1.52)	0.061
Strontium ranelate	140	13/121	10.7	0.78 (0.45-1.35)	0.379	61/517	11.8	0.88 (0.69-1.14)	0.338
Teriparatide	27	0/23	0	-	-	2/59	3.4	0.26 (0.07-1.04)	0.058
Stratified by drug class									
Bisphosphonate	3529	166/3312	5	0.37 (0.32-0.43)	<0.001	1167/15349	7.6	0.57 (0.54-0.61)	<0.001
Non-bisphosphonate	371	43/304	14.1	1.03 (0.77-1.4)	0.831	156/1205	12.9	0.97 (0.83-1.14)	0.732
PS trimming^	3705	203/3602	5.6	0.4 (0.35-0.46)	<0.001	1338/17463	7.7	0.56 (0.53-0.59)	<0.001

Abbreviations: py person-year; HRT hormone replacement therapy; PS propensity score

^excluded treated patients with PS below 5% of that in treated group or untreated patients with PS above 95% of that in untreated group.

# B) CVD mortality

Group	Short-term					Long-term				
	N	No. of death/py	Mortality rate, per 100 py	Relative risk (95% CI)	P	N	No. of death/py	Mortality rate, per 100 py	Relative risk (95% CI)	P
Untreated	28545	735/28085	2.6	-	-	16528	2659/86556	3.1	-	-
Treated	3739	56/3709	1.5	0.58 (0.44-0.76)	<0.001	2671	249/14265	1.7	0.56 (0.49-0.63)	<0.001
Stratified by individual drug										
Alendronate	2645	32/2558	1.3	0.48 (0.34-0.68)	<0.001	2002	164/9391	1.7	0.54 (0.46-0.64)	<0.001
Ibandronate	522	7/469	1.5	0.57 (0.27-1.2)	0.136	370	32/1864	1.7	0.56 (0.4-0.8)	0.001
Risedronate	104	1/93	1.1	0.41 (0.06-2.91)	0.371	78	4/401	1	0.34 (0.13-0.9)	0.03
Zoledronate	132	0/127	0	-	-	114	2/393	0.5	0.15 (0.04-0.59)	0.007
Denosumab	30	1/28	3.6	1.36 (0.19-9.65)	0.76	26	2/71	2.8	0.77 (0.19-3.07)	0.708
Raloxifene	5	0/5	0	-	-	4	0/21	0	-	-
HRT	1	0/1	0	-	-	1	0/10	0	-	-
Salcatonin	148	9/119	7.6	2.85 (1.48-5.51)	0.002	95	13/275	4.7	1.46 (0.85-2.52)	0.173
Strontium ranelate	132	5/118	4.2	1.61 (0.67-3.88)	0.289	94	15/379	4	1.24 (0.74-2.05)	0.415
Teriparatide	27	0/23	0	-	-	25	0/50	0	-	-
Stratified by drug class										
Bisphosphonate	3403	40/3246	1.2	0.47 (0.34-0.65)	<0.001	2564	202/12049	1.7	0.53 (0.46-0.61)	<0.001
Non-bisphosphonate	343	15/294	5.1	1.93 (1.16-3.23)	0.011	245	30/806	3.7	1.14 (0.79-1.63)	0.487
PS trimming^	3555	53/3526	1.5	0.56 (0.43-0.74)	<0.001	2589	222/13628	1.6	0.49 (0.43-0.56)	<0.001

Abbreviations: py person-year; HRT hormone replacement therapy; PS propensity score

^excluded treated patients with PS below 5% of that in treated group or untreated patients with PS above 95% of that in untreated group.

Table 3 Risk estimate of mortality in patients treated with anti-osteoporosis medications after propensity score matching

A) All-cause mortality

Group	N	Short-term				Long-term			
		No. of death/py	Mortality rate, per 100 py	Relative risk (95% CI)	P	No. of death/py	Mortality rate, per 100 py	Relative risk (95% CI)	P
Untreated	7800	810/7334	11	-	-	3442/32132	10.7	-	-
Treated	3900	217/3788	5.7	0.52 (0.45-0.6)	<0.001	1478/18599	7.9	0.74 (0.69-0.78)	<0.001
Stratified by individual drug									
Alendronate	2739	126/2608	4.8	0.44 (0.36-0.53)	<0.001	901/11852	7.6	0.71 (0.66-0.76)	<0.001
Ibandronate	541	26/479	5.4	0.49 (0.33-0.73)	<0.001	203/2532	8	0.73 (0.64-0.85)	<0.001
Risedronate	108	5/95	5.3	0.47 (0.2-1.14)	0.095	34/518	6.6	0.6 (0.43-0.84)	0.003
Zoledronate	141	9/130	6.9	0.63 (0.32-1.21)	0.161	29/447	6.5	0.62 (0.43-0.9)	0.012
Denosumab	30	1/28	3.6	0.32 (0.05-2.3)	0.259	6/79	7.6	0.75 (0.34-1.67)	0.481
Raloxifene	7	2/6	33.3	2.85 (0.71-11.4)	0.14	3/28	10.7	0.98 (0.32-3.05)	0.978
HRT	1	0/1	0	-	-	0/10	0	-	-
Salcatonin	166	27/124	21.8	1.95 (1.33-2.87)	<0.001	84/513	16.4	1.52 (1.23-1.89)	<0.001
Strontium ranelate	140	13/121	10.7	0.97 (0.56-1.67)	0.903	61/517	11.8	1.1 (0.85-1.42)	0.458
Teriparatide	27	0/23	0	-	-	2/59	3.4	0.33 (0.08-1.33)	0.12
Stratified by drug class									
Bisphosphonate	3529	166/3312	5	0.45 (0.38-0.54)	<0.001	1167/15349	7.6	0.71 (0.66-0.76)	<0.001
Non-bisphosphonate	371	43/304	14.1	1.28 (0.94-1.73)	0.12	156/1205	12.9	1.21 (1.03-1.42)	0.019
PS trimming^	3705	203/3602	5.6	0.53 (0.46-0.62)	<0.001	1338/17463	7.7	0.72 (0.67-0.77)	<0.001

Abbreviations: py person-year; HRT hormone replacement therapy; PS propensity score

^excluded treated patients with PS below 5% of that in treated group or untreated patients with PS above 95% of that in untreated group.

## B) CVD mortality

Group	Short-term					Long-term				
	N	No. of death/py	Mortality rate, per 100 py	Relative risk (95% CI)	P	N	No. of death/py	Mortality rate, per 100 py	Relative risk (95% CI)	P
Untreated	7149	159/7041	2.3	-	-	4884	526/23750	2.2	-	-
Treated	3739	56/3709	1.5	0.67 (0.49-0.91)	0.01	2671	249/14265	1.7	0.8 (0.69-0.93)	0.003
Stratified by individual drug										
Alendronate	2645	32/2558	1.3	0.55 (0.38-0.81)	0.002	2002	164/9391	1.7	0.78 (0.66-0.93)	0.007
Ibandronate	522	7/469	1.5	0.66 (0.31-1.41)	0.28	370	32/1864	1.7	0.8 (0.56-1.15)	0.227
Risedronate	104	1/93	1.1	0.47 (0.07-3.39)	0.458	78	4/401	1	0.47 (0.18-1.27)	0.137
Zoledronate	132	0/127	0	-	-	114	2/393	0.5	0.21 (0.05-0.86)	0.03
Denosumab	30	1/28	3.6	1.58 (0.22-11.25)	0.651	26	2/71	2.8	1.14 (0.28-4.57)	0.855
Raloxifene	5	0/5	0	-	-	4	0/21	0	-	-
HRT	1	0/1	0	-	-	1	0/10	0	-	-
Salcatonin	148	9/119	7.6	3.32 (1.7-6.5)	<0.001	95	13/275	4.7	2.09 (1.2-3.62)	0.009
Strontium ranelate	132	5/118	4.2	1.87 (0.77-4.55)	0.168	94	15/379	4	1.78 (1.07-2.98)	0.027
Teriparatide	27	0/23	0	-	-	25	0/50	0	-	-
Stratified by drug class										
Bisphosphonate	3403	40/3246	1.2	0.55 (0.39-0.77)	<0.001	2564	202/12049	1.7	0.76 (0.64-0.89)	<0.001
Non-bisphosphonate	343	15/294	5.1	2.25 (1.32-3.82)	0.003	245	30/806	3.7	1.64 (1.14-2.37)	0.008
PS trimming^	3555	53/3526	1.5	0.69 (0.51-0.95)	0.022	2589	222/13628	1.6	0.76 (0.65-0.89)	<0.001

Abbreviations: py person-year; HRT hormone replacement therapy; PS propensity score

^excluded treated patients with PS below 5% of that in treated group or untreated patients with PS above 95% of that in untreated group.

Table 4 Risk estimate of CVD mortality in patients after propensity score matching, stratified by baseline CVD

## A) Patients without baseline CVD

Group	Short-term					Long-term				
	N	No. of death/py	Mortality rate, per 100 py	Relative risk (95% CI)	P	N	No. of death/py	Mortality rate, per 100 py	Relative risk (95% CI)	P
Untreated	5419	77/5362	1.4	-	-	3715	285/18379	1.6	-	-
Treated	2808	31/2790	1.1	0.77 (0.51-1.17)	0.229	2071	136/11361	1.2	0.78 (0.64-0.96)	0.019
Stratified by individual drug										
Alendronate	2016	18/1951	0.9	0.64 (0.38-1.07)	0.091	1559	88/7504	1.2	0.76 (0.6-0.96)	0.022
Ibandronate	378	3/336	0.9	0.62 (0.2-1.96)	0.414	284	15/1487	1	0.68 (0.4-1.14)	0.14
Risedronate	85	1/74	1.4	0.93 (0.13-6.7)	0.944	68	2/343	0.6	0.39 (0.1-1.57)	0.185
Zoledronate	93	0/88	0	-	-	82	1/288	0.3	0.21 (0.03-1.53)	0.125
Denosumab	23	0/22	0	-	-	19	0/54	0	-	-
Raloxifene	4	0/4	0	-	-	3	0/20	0	-	-
HRT	1	0/1	0	-	-	1	0/10	0	-	-
Salcatonin	103	6/84	7.1	4.96 (2.16-11.38)	<0.001	66	8/184	4.3	2.73 (1.35-5.51)	0.005
Strontium ranelate	87	3/78	3.8	2.67 (0.84-8.45)	0.096	66	10/278	3.6	2.33 (1.24-4.37)	0.009
Teriparatide	21	0/19	0	-	-	19	0/44	0	-	-
Stratified by drug class										
Bisphosphonate	2572	22/2450	0.9	0.62 (0.39-1)	0.052	1993	106/9621	1.1	0.71 (0.57-0.89)	0.003
Non-bisphosphonate	239	9/207	4.3	3.01 (1.51-6)	0.002	174	18/589	3.1	1.93 (1.2-3.12)	0.007

Abbreviations: py person-year; HRT hormone replacement therapy; PS propensity score

B) Patients with baseline CVD

Group	Short-term					Long-term				
	N	No. of death/py	Mortality rate, per 100 py	Relative risk (95% CI)	P	N	No. of death/py	Mortality rate, per 100 py	Relative risk (95% CI)	P
Untreated	1738	73/1699	4.3	-	-	1068	208/4597	4.5	-	-
Treated	931	25/919	2.7	0.63 (0.4-1)	0.048	600	113/2905	3.9	0.87 (0.69-1.1)	0.247
Stratified by individual drug										
Alendronate	629	14/607	2.3	0.54 (0.3-0.95)	0.033	443	76/1887	4	0.88 (0.67-1.14)	0.326
Ibandronate	144	4/133	3	0.7 (0.26-1.93)	0.494	86	17/378	4.5	1.04 (0.63-1.7)	0.887
Risedronate	19	0/18	-	-	-	10	2/58	3.4	0.92 (0.23-3.7)	0.905
Zoledronate	39	0/38	-	-	-	32	1/105	1	0.19 (0.03-1.35)	0.096
Denosumab	7	1/6	16.7	3.81 (0.53-27.4)	0.184	7	2/18	11.1	2.18 (0.54-8.79)	0.273
Raloxifene	1	0/1	-	-	-	1	0/1	0	-	-
HRT	0	0/	-	-	-	0	0/	-	-	-
Salcatonin	45	3/35	8.6	2 (0.63-6.33)	0.241	29	5/90	5.6	1.33 (0.55-3.23)	0.529
Strontium ranelate	45	2/40	5	1.17 (0.29-4.75)	0.83	28	5/101	5	1.1 (0.45-2.67)	0.837
Teriparatide	6	0/4	0	-	-	6	0/7	0	-	-
Stratified by drug class										
Bisphosphonate	831	18/796	2.3	0.53 (0.31-0.88)	0.015	571	96/2427	4	0.87 (0.68-1.11)	0.252
Non-bisphosphonate	104	6/87	6.9	1.63 (0.71-3.74)	0.253	71	12/217	5.5	1.24 (0.69-2.22)	0.466

Figure 1 Case selection chart

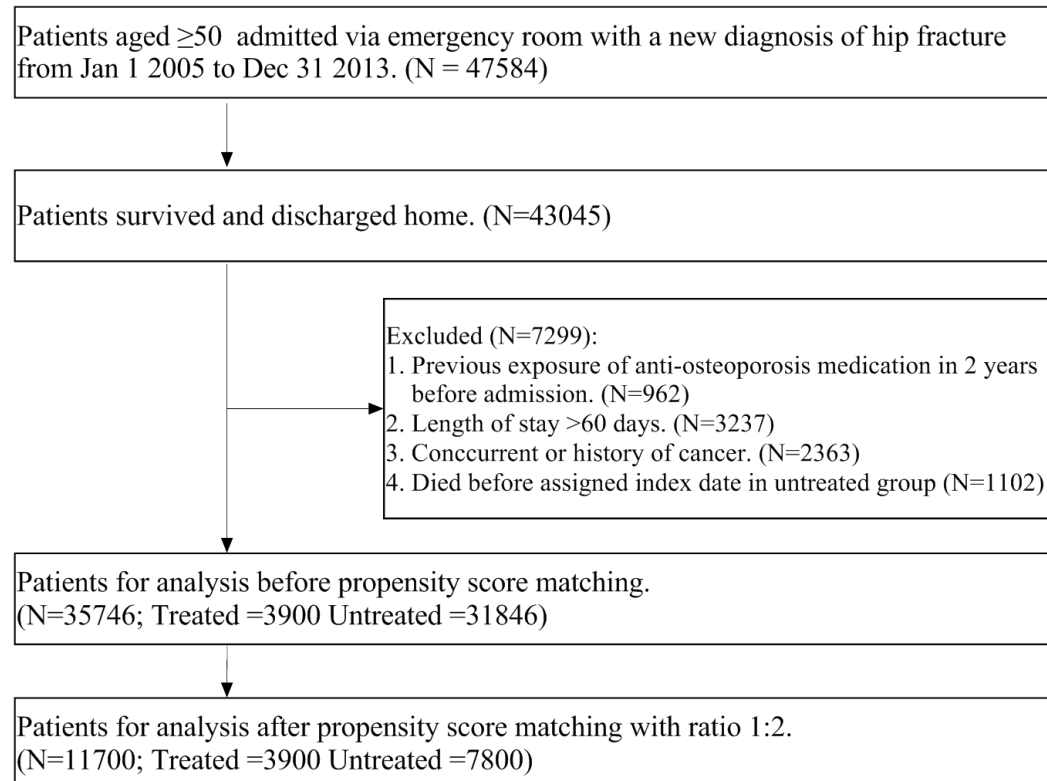




Figure 2 Propensity score distribution before and after matching

